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Letters to the Editor

Difference in Therapeutic Response Between Basal and Nonbasal Triple-Negative Breast Cancers

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Disclosures of potential conflicts of interest may be found at the end of this article.

The study described here, which nicely complements a study by Prat et al. that was recently published in ***The Oncologist***, shows for the first time that triple-negative breast cancers are much more heterogeneous than basal breast cancers regarding the response to chemotherapy and the probability of response to molecularly targeted therapies.

Prat et al. report that triple-negative (TN) breast cancers (BCs) represent a more heterogeneous group than basal BCs [1]. TN BCs include basal and nonbasal tumors and show much more difference in patient age and gene expression profiles than basal BCs, which include TN and non-TN cases. These results confirm our previous observations [2] reported in a smaller series with several tumor features: age; pathological grade; mRNA expression of *ESR1*, *PGR*, and *ERBB2* and markers of luminal (*KRT18*) and basal (*KRT5* and *KRT6A*) epithelial lineage. Current efforts aim to define better systemic therapies for TN BCs [3, 4]. In this context, an important issue— even more relevant clinically than histological and molecular characterization—is whether this difference of homogeneity between TN BCs and basal BCs exists in terms of therapeutic response.

We tested this hypothesis in a large gene expression database of BCs including 33 public microarray data sets, representing 6,717 invasive BCs that were clinically annotated. A total of 645 samples were TN according to their immunohistochemistry status, and 584 were basal according to the PAM50 and claudin-low predictors [5, 6]. Within TN BCs, 315 were basal and 330 were nonbasal. Within basal BCs, 330 were TN and 255 were non-TN. Univariate analyses (Table 1) compared several histoclinical and molecular variables related to therapeutic response in the two TN subgroups (basal vs. nonbasal) and in the two basal subgroups (TN vs. non-TN).

The rate of pathological complete response (pCR) to neoadjuvant anthracycline-based chemotherapy was 33% in the 324 informative TN cases and 38% in the 226 informative basal cases. More important, the pCR rate and all tested variables classically linked to chemosensitivity (pathological tumor size, genomic grade index, *MKI67* mRNA expression) were very different between the two TN subgroups but were not different between the two basal subgroups. Among the TN BCs, higher pCR rate, smaller pT3 size, higher genomic grade index, and *MKI67* mRNA expression were found in basal samples compared with nonbasal samples.

We observed similar results with targets of molecularly targeted therapies under development for TN BCs. To exploit the DNA repair defect observed within basal BCs, poly (ADP-ribose) polymerase or "PARP" inhibitors have been evaluated in TN BCs. Initial promising results with olaparib [7] did not hold in the following phase III trial that enrolled 519 TN patients [8]. One explanation was the absence of proper patient selection. Our present analysis reinforces this hypothesis: The genome instability, assessed by the Carter's gene expression signature, *PARP1* mRNA expression, or gene expression signature of homologous recombination and *ATR-BRCA* pathway, was much more heterogeneous in TN BCs than in basal BCs. Similarly, the activation status of 18 biological pathways [9] including potential therapeutic targets of TN BCs (i.e., EGFR, PIK3CA [also known as PI3K], or SRC) or therapeutic response-associated markers (i.e., TP53 [also known as P53], TP63 [also known as P63], or KRAS) was much more homogeneous in basal BCs.

We show that TN BCs are much more heterogeneous than basal BCs regarding the response to chemotherapy and the probability of response to targeted therapies. This result, together with the study by Prat et al. [1], calls for caution in the interpretation and design of clinical trials dedicated to otherwise nonspecified TN BCs and warrants the search for molecular markers of basal BCs that are more clinically applicable than gene expression profiling.

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Disclosures

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Table 1. Comparison of breast cancer subgroups within the triple-negative group and the basal group

	TN breast cancers (n = 645)				Basal breast cancers (n = 585)			
Variable	n	Non-basal subgroup (n = 315)	Basal subgroup (n = 330)	p[a]	n	Non-TN subgroup (n = 255)	TN subgroup (n = 330)	p[a]
Pathological complete response	324			3.22E-03	226			.229
No	216	122 (74%)	94 (59%)		139	45 (68%)	94 (59%)	
Yes	108	42 (26%)	66 (41%)		87	21 (32%)	66 (41%)	
Pathological tumor size	267			3.51E-02	272			.406
pT1	67	38 (28%)	29 (22%)		69	40 (29%)	29 (22%)	
pT2	148	64 (48%)	84 (63%)		163	79 (57%)	84 (63%)	
pT3	52	32 (24%)	20 (15%)		40	20 (14%)	20 (15%)	
Genomic grade index	608			8.86E-16	520			.870
High	479	195 (65%)	284 (92%)		478	194 (92%)	284 (92%)	
Low	129	103 (35%)	26 (8%)		42	16 (8%)	26 (8%)	
MKI67 mRNA expression[b]	644	3.07	3.87	3.60E-15	584	3.56	3.87	7.18E-03
PARP1 mRNA expression[b]	645	0.36	0.72	1.34E-14	585	0.72	0.72	.840
Homologous recombination (KEGG pathway)[c]	645	0.13	0.38	1.91E-24	585	0.32	0.38	3.21E-02
ATR-BRCA pathway (Biocarta)[c]	645	0.23	0.48	4.80E-18	585	0.43	0.48	.075
Carter's gene expression signature	645			2.49E-18	585			.354
Stable	187	141 (45%)	46 (14%)		89	43 (17%)	46 (14%)	
Unstable	458	174 (55%)	284 (86%)		496	212 (83%)	284 (86%)	
AKT[d]	645	0.53	0.56	4.07E-02	585	0.51	0.56	8.78E-03
BCAT[d]	645	0.48	0.84	4.26E-24	585	0.8	0.84	.060
E2F1[d]	645	0.51	0.65	1.46E-07	585	0.62	0.65	.391
EGFR[d]	645	0.55	0.37	2.66E-12	585	0.42	0.37	.094
ER[d]	645	0.07	0.02	7.03E-17	585	0.04	0.02	1.03E-08
HER2[d]	645	0.47	0.42	1.18E-03	585	0.49	0.42	2.17E-03
IFNα[d]	645	0.6	0.63	.147	585	0.73	0.63	.395
IFNγ[d]	645	0.7	0.75	.330	585	0.81	0.75	.355
MYC[d]	645	0.45	0.73	9.43E-34	585	0.66	0.73	1.95E-03
TP53[d]	645	0.21	0.1	1.86E-26	585	0.12	0.1	2.37E-05
PIK3CA[d]	645	0.47	0.62	1.10E-12	585	0.59	0.62	.184
PR[d]	645	0.06	0.05	8.44E-07	585	0.07	0.05	9.74E-11
SRC[d]	645	0.49	0.4	9.65E-04	585	0.4	0.4	.864
STAT3[d]	645	0.56	0.48	8.57E-09	585	0.5	0.48	.282
TGFβ[d]	645	0.52	0.36	2.30E-07	585	0.44	0.36	4.17E-02
TP63[d]	645	0.54	0.63	7.96E-07	585	0.57	0.63	2.58E-03
KRAS[d]	645	0.52	0.67	2.10E-19	585	0.62	0.67	8.64E-03
TNFα[d]	645	0.67	0.72	0.092	585	0.68	0.72	0.428

[a]Fisher's exact test for qualitative variables with discrete categories, and Wilcoxon test for continuous variables. p values under 5% are displayed with the E notation, where E represents times 10 raised to the power of the following exponent.
[b]Mean mRNA expression of Affymetrix (Santa Clara, CA, http://www.affymetrix.com) probeset ID: 205225_at for *MKI67*, 208305_at for *PARP1*.
[c]Mean metagene score.
[d]Mean activation score.
Abbreviation: TN, triple negative.

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Editor's Note: Drs. Prat et al. have reviewed this letter and agree with the reported findings but have chosen not to respond formally.

